Review

# The LAN blood group system: a review

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LAN (Langereis) was officially recognized by the International Society of Blood Transfusion in 2012 as being the 33rd human blood group system. It consists of one single high-prevalence antigen, Lan (LAN1). The ABCB6 protein is the carrier of the Lan blood group antigen. The *ABCB6* gene (chromosome 2q36, 19 exons) encodes the ABCB6 polypeptide (ATP-binding cassette protein, subfamily B, member 6), known as a porphyrin transporter. The exceptional Lan– people do not express ABCB6 (Lan null phenotype), owing to several different molecular mechanisms affecting *ABCB6:* frameshift leading to a premature stop codon (deletion, insertion, or nonsense mutation of nucleotides); missense mutation; or intronic mutation responsible for RNA splicing defect. Despite the Lan antigen's being reported to play a key role in erythropoiesis and detoxification of cells, Lan– people do not appear to demonstrate susceptibility to any disease or seemingly physiologic disorder. Anti-Lan has been described as having variable clinical significance, either for hemolytic transfusion reactions (none to severe) or hemolytic disease of the fetus and newborn (none to mild). Despite challenging conditions caused by the scarcity of Lan– donors worldwide, Lan– blood should ideally be given to patients with anti-Lan, especially those with a high-titer antibody. ***Immunohematology* 2013;29:131–135.**

**Key Words:** immunohematology, transfusion, red blood cells, rare blood type, Lan blood group, ABCB6, ABC transporter, ATP binding cassette

## History

In 1962, van der Hart and collaborators described an antibody to a high-prevalence red blood cell (RBC) antigen responsible for a severe and acute hemolytic transfusion reaction.[1] The corresponding antigen, Lan, was named for the index case, Mr. Langereis (Dutch origin), whose brother was also found to be Lan–. The antibody of the proband was described to be nonreactive with only one random donor in 4000 tested in the population of the Netherlands.

Many examples of anti-Lan in people with the rare Lan– phenotype were later reported.[2–10] Two high-prevalence antigens, $Gn^a$ and So, described in 1969 and 1970, respectively, were subsequently shown to be the same as Lan.[4,11–13]

## Terminology and Nomenclature

In 1990, the Working Party on Terminology for Red Cell Surface Antigens of the International Society of Blood Transfusion (ISBT) decided to place Lan in the 901 series of RBC antigens, with reference number 901.002.[14] The 901 series corresponds to a family of RBC antigens with a prevalence greater than 90 percent in the general population, for which data about their genetic independence from other known blood group antigens and about their molecular basis are nonexistent.[15]

As a result of the discovery of its molecular basis in January 2012 by Helias and collaborators,[16] LAN was officially moved in July 2012 from the 901 series to the novel 33rd blood group system, LAN, by the ISBT Working Party on Red Cell Immunogenetics and Blood Group Terminology (ISBT World Meeting, Cancun, Mexico).[17] The LAN blood group system contains one single antigen to date, LAN1.

## Genetics and Inheritance

Lan is a high-prevalence antigen in most populations (> 99.9%), and Lan– is considered a rare blood type worldwide.[18,19] Prevalence of the Lan– type was estimated to be approximately 1 in 20,000 in Caucasians,[18,20] 1 in 50,000 in Japanese,[6] and 1 in 1500 in black people from South Africa.[8] Anti-Lan has also been described in two African Americans.[3,10] The Lan– phenotype is inherited as a recessive character.

In France, 10 of the 29 Lan– people (35%) registered in the national rare blood database originate from the Maghreb area in North Africa (unpublished observations).

## Molecular Basis of Lan

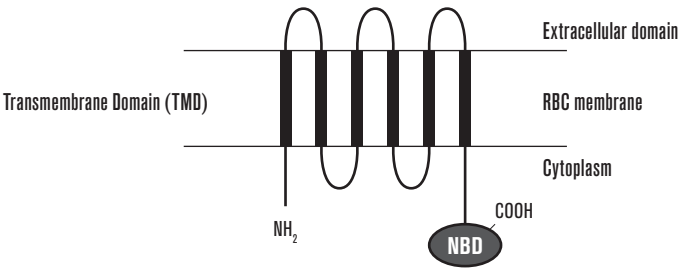
Helias and collaborators[16] used a monoclonal anti-Lan available from a Japanese team, clone OSK43,[21] to elucidate the molecular basis of Lan (of note, no commercial anti-Lan typing reagent is available on the market). A biochemical approach, combining an immunoprecipitation test and mass spectrometry analysis, showed that the ABCB6 transporter carries the Lan antigen.

The adenosine triphosphate (ATP)-binding cassette (ABC) superfamily represents the largest and most broadly expressed class of proteins in all kingdoms of life.[22] ABC proteins are able to transport a variety of biologic compounds through ATP hydrolysis. ABCB6 (initially named MTABC3

for mammalian-mitochondrial ABC protein 3) is an ATP-binding cassette molecule, subfamily B, member 6, known as a porphyrin transporter, which was initially described to be located in the outer membrane of mitochondria.[23,24] It was later reported that ABCB6 expression could be restricted to the Golgi apparatus,[25] lysosomes, and plasma membranes.[26] However, this appears controversial because ABCB6 was recently purified from mitochondrial membrane extracts.[27] Until the discovery of the molecular basis of LAN, ABCB6 was quite surprisingly not reported to be present in the erythrocyte membrane.

The *ABCB6* gene is located on chromosome 2q36. It spans approximately 9.2 kb of genomic DNA, consists of 19 exons (3021-bp cDNA; GenBank access number NM_005689; Entrez Gene ID 10058), and encodes an 842 multipass amino acid protein (80 kDa), ABCB6, with eight membrane-spanning α-helices.[28] ABCB6 belongs to the so-called half-transporter family within ABC transporters; it contains one transmembrane domain (TMD) and one nucleotide-binding domain (NBD; Fig 1). The NBD domain binds and hydrolyzes ATP; it is located at the C-terminal end of the ABCB6 polypeptide and includes three characteristic motifs: an LSGGQ conserved signature sequence (specific to ABC transporters)[29] flanked by Walker A and Walker B consensus motifs (common to many nucleic acid–dependent ATPases).[30] The minimal functional molecular unit of ABCB6 has been suggested to be a homodimer.[23,31] Because ABCB6 has been proposed to regulate heme synthesis by shuttling coproporphyrinogen III from the cytoplasm into the mitochondria, it is believed to play a crucial role in erythropoiesis.[23,27,32] ABCB6 has also been reported to represent a protective mechanism against oxidative cellular stress.[33] Finally, ABCB6 has been suggested to be involved in cell growth and proliferation by targeting the cell cycle.[34]

The precise role of ABCB6 in the RBC membrane remains unclear. Because the plasma level of porphyrins was found to be very low in four Lan– individuals, ABCB6 is thought to export porphyrins out of RBCs, which may prevent their intracellular accumulation.[16]




NBD: Nucleotide Binding Domain, involved in the binding and hydrolysis of ATP

**Fig. 1** ABCB6 transporter at the red blood cell surface.

People with the rare Lan– phenotype are actually Lan null or *ABCB6–/–* (two nonfunctional *ABCB6* alleles) and may therefore be considered as "human knockouts" for *ABCB6*. Lan– individuals demonstrate different inactivating molecular mechanisms of *ABCB6* at homozygous or compound heterozygous states: frameshift leading to a premature stop codon (deletion, insertion, or nonsense mutation of nucleotides), missense mutation, or intronic mutation responsible for RNA splicing defect.

Multiple null alleles of *ABCB6* have been reported to date, as shown in Table 1. In addition, a few altered alleles of *ABCB6* were recently shown to encode a weak expression of Lan (Table 2).[35] This may explain why a significant proportion of people who are only weakly positive for Lan may be mistyped as Lan– if a potent anti-Lan is not used.[38]

The ISBT has proposed a numbering system for *ABCB6* alleles encoding for null and altered phenotypes (see Web site Names for LAN Blood Group Alleles v2.0 130208 http://www.isbtweb.org/fileadmin/user_upload/WP_on_Red_Cell_Immunogenetics_and/LAN_Alleles_v2_0__130211.pdf). The reference allele encoding Lan is named *ABCB6*01*. As of today, *ABCB6* null alleles are numbered from *ABCB6*01N.01* to *ABCB6*01N.15* (N for null) and altered alleles *ABCB6*01W.01* to *ABCB6*01W.04* (W for weak); for an update, see Web site http://www.isbtweb.org/working-parties/red-cell-immunogenetics-and-blood-group-terminology/blood-group-terminology/blood-group-allele-terminology/ from the ISBT Working Party on Red Cell Immunogenetics and Blood Group Terminology.

*ABCB6* mutations have been found in some rare genetic diseases, such as ocular coloboma,[39] autosomal dominant familial pseudohyperkalemia,[40] and dyschromatosis universalis hereditaria (so called "gain-of-function" mutations).[41] However, all Lan– people reported to date were seemingly healthy, experiencing no clinical symptoms of porphyria or abnormal complete blood count.[16] As a result, ABCB6 is known not to be a protein essential for life in humans, and it does not appear to be fully required for erythropoiesis.[16] An alternative pathway for porphyrin transport very likely exists, probably through ABCG2,[42] another ABC protein that recently has been shown to carry the JR blood group sytem antigens.[43]

## Biochemistry and Physiology

LAN shows a wide tissue distribution and has been reported to be highly expressed in fetal liver, heart, eye, and

**Table 1.** List of reported *ABCB6* null alleles that encode the Lan– phenotype[18,35]

| Nucleotide change | Location | Predicted protein change | Ethnic background | References | Allele number proposed by ISBT |
|---|---|---|---|---|---|
| c.197_198insG | Exon 1 | p.Ala66Gly fs stop | Caucasian | Helias et al.[16] | *ABCB6*01N.01* |
| c.85_87delTTC | Exon 1 | p.Phe29del | Caucasian | Saison et al.[36] | *ABCB6*01N.14* |
| c.376delG | Exon 1 | p.Val126Ser fs stop | African | Reid et al.,[35] Zelinski et al.[37] | *ABCB6*01N.15* |
| c.574C>T | Exon 2 | Arg192Trp | North African | Saison et al.,[36] Reid et al.,[35] Zelinski et al.[37] | *ABCB6*01N.13* |
| c.717G>A | Exon 3 | p.Gln239 stop | Caucasian | Helias et al.[16] | *ABCB6*01N.02* |
| c.953_956delGTGG | Exon 4 | p.Gly318Ala fs stop | Caucasian | Helias et al.[16] | *ABCB6*01N.03* |
| c.1236G>A | Exon 6 | p.Trp412 stop | African | Reid et al.,[35] Zelinski et al.[37] | *ABCB6*01N.11* |
| c.1533_1543dupCGGCTCCCTGC | Exon 9 | p.Leu515Pro fs stop | Caucasian | Helias et al.[16] | *ABCB6*01N.04* |
| c.1558_1559insT | Exon 9 | p.Val520Cys fs stop | Unknown | Reid et al.,[35] Zelinski et al.[37] | *ABCB6*01N.12* |
| c.1709_1710delAG | Exon 11 | p.Glu570Gly fs stop | Caucasian | Helias et al.[16] | *ABCB6*01N.05* |
| c.1690_1691delAT | Exon 11 | p.Met564Val fs stop | Japanese | Helias et al.[16] | *ABCB6*01N.06* |
| c.1867delinsAACAGGTGA | Exon 14 | p.Gly623Asn fs stop | Caucasian | Helias et al.[16] | *ABCB6*01N.07* |
| c.1942C>T | Exon 14 | p.Arg648 stop | Caucasian | Helias et al.[16] | *ABCB6*01N.08* |
| c.1985_1986delTC | Exon 15 | p.Leu662Pro fs stop | Caucasian | Helias et al.[16] | *ABCB6*01N.09* |
| c.2256 + 2t>g | Intron 16 | RNA splicing defect | Caucasian | Helias et al.[16] | *ABCB6*01N.10* |

**Table 2.** List of reported *ABCB6* alleles that encode the Lan weak phenotype[18,35]

| Nucleotide change | Location | Predicted protein change | Ethnic background | References | Allele number proposed by ISBT |
|---|---|---|---|---|---|
| c.826C>T | Exon 3 | p.Arg276Trp | Caucasian | Reid et al.,[35] Saison et al.,[36] Zelinski et al.[37] | *ABCB6*01W.01* |
| c.1028G>A | Exon 5 | p.Arg343Gln | African | Reid et al.,[35] Zelinski et al.[37] | *ABCB6*01W.02* |
| c.1762G>A | Exon 12 | p.Gly588Ser | Caucasian | Reid et al.,[35] Saison et al.,[36] Zelinski et al.[37] | *ABCB6*01W.03* |
| c.2216G>A | Exon 16 | p.Arg739His | Hispanic | Reid et al.,[35] Zelinski et al.[37] | *ABCB6*01W.04* |

skeletal muscle.[44] Cord RBCs show a higher Lan reactivity than adult cells.[16]

Lan is resistant to the treatment of RBCs by papain, ficin, trypsin, α-chymotrypsin, dithiothreitol (DTT) 200 mM, pronase, neuraminidase, and EDTA/glycine/acid.[19]

## Antibodies in the System and Clinical Significance

Anti-Lan may be stimulated by RBC transfusion or pregnancy. No naturally occurring anti-Lan has been reported to date.[17] Lan alloantibodies are mostly a mix of immunoglobulin (Ig) G1 and IgG3, but IgG1 or IgG3 alone has also been described, as well as IgG2 and IgG4 components.[6,45–47] Anti-Lan may fix complement.[1,6,9]

One case of autoanti-Lan has been reported in a female patient with a mild autoimmune hemolytic anemia.[48] Anti-Lan was reactive 3+ by indirect antiglobulin test. The direct antiglobulin test was weakly positive (1+), and anti-Lan could be eluted from autologous RBCs. The patient's RBCs showed a significant weakening of Lan expression.

Anti-Lan has been described as having variable clinical significance.[18–20,49] It may cause hemolytic transfusion reactions, ranging from none to severe,[1] and hemolytic disease of the fetus and newborn, ranging from none to mild.[7,9,50] The ability of anti-Lan to cause hemolytic transfusion reaction may be studied by in vitro functional assays, and many examples of anti-Lan were found to have the potential to destroy Lan+ RBCs in vivo.[45,49] The reactivity of anti-Lan was reported to often be enhanced in the in-vitro monocyte monolayer assay when fresh serum is added to anti-Lan at the time of the test.[51]

Despite challenging conditions caused by scarcity of Lan– donors worldwide,[52,53] Lan– RBC units should ideally be selected for the transfusion of Lan– patients with anti-Lan, especially those with a high-titer antibody.[54]

## Summary and Perspectives

The ABCB6 protein recently has been shown to carry the Lan antigen. The new system LAN (Langereis), number 33 according to ISBT, currently contains one single antigen, Lan (LAN1), with a prevalence greater than 99.9 percent in most populations. Lan– (LAN:–1) people do not express *ABCB6* (Lan null phenotype). LAN remains a difficult blood group system to investigate because no commercial anti-Lan is available and no routine molecular testing exists for Lan genotyping. Implementation of Lan typing in the currently available high-throughput genotyping devices will be quite challenging because of the high number of null alleles of *ABCB6* to be simultaneously tested (15 reported to date). In addition, full sequencing of *ABCB6* is costly and labor intensive (19 exons). The so-called next-generation sequencing platforms will likely be helpful to overcome this problem in the future. Finally, the LAN blood group system, as well as JR,[55] turns out to be a typical and striking example of the quite unexpected close relationships between the immunohematology, pharmacology, and oncology fields.

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